REMARKS

Applicants acknowledge that the Examiner has maintained the Restriction Requirement (Paper No. 7), dated October 1, 2001, over Applicants' traverse. Accordingly, Claims 6-8, 56, and 57 have been withdrawn by the Examiner. Applicants reserve the right to prosecute the withdrawn claims in a subsequent divisional application.

Applicants have amended paragraphs in Example 17 of the specification at p. 34, line 27-p. 35, line 30 of the specification (after the title of the Example) to provide indicia of trademarks and corresponding generic terms not previously so identified in the specification. In particular, RNEASY® is a trademark of QIAGEN GmbH (Hilden, Germany) for RNA isolation kits and SARTOLON® is a trademark of Sartorius for a polyamide filter membrane.

Applicants have amended the claims to direct coverage in this application to a preferred embodiment of the invention, i.e., to a process for isolating nucleic acids wherein the nucleic acids are immobilized, released, and removed from one and the same side of a non-siliceous surface. Accordingly, recitations of siliceous surfaces, siliceous membranes, siliceous compounds (e.g., silicones), etc., have been deleted from the claims. Applicants reserve the right to prosecute such embodiments of the invention in a subsequent divisional or continuation application.

Applicants have also amended the claims to correct dependencies, to eliminate improper multiple dependent claiming, to correct grammatical syntax, to maintain consistency in use of terms throughout the claims, and to correct claim language for Markush-type claiming as discussed below.

Applicants have amended Claims 1 and 2 to clearly cover a preferred embodiment of the invention which provides a process for isolating nucleic acids comprising charging a non-siliceous surface, wherein the non-siliceous surface has two opposing sides and the nucleic acids are charged on, immobilized on, released from (eluted), and removed from the same side of the non-siliceous surface. Support for the amendments is found in original Claims 1 and 2 and also throughout the specification. See, e.g., p. 5, lines 4-7; p. 6, lines 2-4; p. 11, lines 6-13; p. 15, line 7-p. 16, line 2; and Figures 2-4 of the specification depicting immobilization and elution of nucleic acids from the same side of a surface according to the invention. See, also, p. 16, lines 3-8, and also Examples 1-19 at p. 16, line 10-p. 36, line 15, of the specification for examples

describing the use of various non-siliceous surfaces. Accordingly, the amendments add no new matter.

The term "non-siliceous" has been added to dependent Claims 4 and 5 to maintain a consistent use of terms throughout all dependent claims. Accordingly, the amendments add no new matter.

To avoid improper multiple dependent claiming, Claim 3 has been amended to depend from Claim 1 alone, Claim 5 has been amended to depend from Claim 1 alone, and Claim 9 has been amended to depend from Claim 1 alone. Accordingly, the amendments add no new matter.

Claim 44 has been amended to depend from Claim 1 instead of Claim 43 (now canceled and which indirectly depended from Claim 1 via canceled Claim 42). Accordingly, the amendment properly adjusts a dependency and adds no new matter.

Claim 9 has also been amended to cover the embodiment of the process according to Claim 1, wherein between the release and the removal steps at least one chemical reaction is carried out on the nucleic acids. Support for the amendment is found in original Claim 9 and the specification (see, e.g., p. 3, line 29-p. 4, line 3 and p. 4, line 29-p. 5, line 1, of the specification). Accordingly, the amendment adds no new matter.

Claim 13 has been amended to adjust grammar to recite terms consistent with the description, i.e., salts "of" monobasic or polybasic acids or polyfunctional organic acids . . ." (see, e.g., p. 7, lines 3-5, of the specification). Accordingly, the amendment adds no new matter.

Claims 14 and 16 have been amended to clearly cover preferred species of the aqueous solutions of salts of polyfunctional organic acids with alkaline or alkaline earth metals. Support for the amendments is found in the specification (see, e.g., p. 7, lines 3-7, of the specification).

Applicants have canceled Claim 23, which recited "a salt solution or a buffer solution pursuant to any one of claims 4 through 22" as a wash buffer useful in the process according to Claim 3. Applicants have also added new Claims 59-63 to clearly cover embodiments of the process according to Claim 3, wherein immobilized nucleic acids are washed with one of several categories of buffers described in the specification. As noted in the specification, certain buffers that may be used to immobilize nucleic acids in a process of the invention (see, e.g., p. 6, line 29-p. 8, line 9 of the specification) may also be employed in the invention as wash buffers (see, e.g., p. 9, lines 23-24 and Examples 1-19 in the specification). Accordingly, new Claims 59-63 add no new matter.

Claim 25 has been amended to correct a misspelling of the term "released" and, thus, the amendment adds no new matter.

Claim 26, which recites a preferred immobilization buffer comprising a chaotropic agent, has been amended to depend from Claim 5, as Claim 5 (not formally recited Claim 3) provides the first antecedent basis for an immobilization buffer. Use of immobilization buffers comprising one or more chaotropic agents in a process of the invention is described in the specification (see, e.g., p. 7, lines 8-22 and Examples 1-7 of the specification). Accordingly, the amendment provides a proper claim dependency and adds no new matter.

Applicants have amended Claims 27, 31, 38, 41, 45, and 49 to place each of the claims in a proper Markush-style format. Accordingly, the amendments to these claims add no new matter.

Applicants have amended Claims 28-31 and 46-49 to remove recitation of superfluous phrases and avoid prolixity in the claims. In particular, the phrase "alone or in combination with other salts" has been deleted from Claims 28-30 and 46-48 as nothing in the description or the claims prevents the use of a solution containing a chaotropic agent alone or in combination with other salts (see, e.g., p. 7, lines 15-22, of the specification). Claims 31 and 49 have been amended to delete the phrase "are used for the immobilization of nucleic acids" as this phrase is redundant. Accordingly, the amendments add no new matter.

Applicants have amended Claims 38 and 54 to place the claims in a proper Markush-style format consistent with the preferred subject matter sought to be claimed in this application. The phrase "characterized by the fact that" has been deleted and replaced with commonly used term "wherein" in both Claims 38 and 54. Claim 38 has also been amended to insert the term "consisting" between the terms "group" and "of". The phrase "optionally in admixture with aluminum or zirconium salts", which modifies the term "metallic soaps" in the group of selected hydrophobic coating agents has been removed from both claims. The preference for metallic soaps in admixture with aluminum or zirconium salts is now claimed separately in a new, multiple dependent Claim 64. The amendments add no new matter.

Applicants have also deleted the term "silicones" from the group of selected hydrophobic coating agents to clearly focus the claims of this application on a process of isolating nucleic acids comprising non-siliceous surfaces. The amendment adds no new matter.

Applicants' invention provides a process particularly adaptable to mechanical and robotic formats (see, e.g., p. 14, line 1-p. 16, line 2 and Figures 1-4, of the specification). With respect to this embodiment of the invention, Applicants have amended Claim 55 to make clear that the claim covers a process for isolating nucleic acids carried out in a plurality of isolation devices installed on a multi-well plate. The amendment is made to improve the syntax of the claim by deleting recitation of the phrase "a plurality of said membranes are incorporated" to properly focus on the process according to independent Claim 51 for isolating nucleic acids, which (according to Claim 55) is carried out in a particular preferred setting, i.e., in a plurality of isolation devices installed on a multi-well plate. A description of carrying out the process of isolating nucleic acids in isolation devices is described in the specification (see, e.g., p. 14, lines 10-18 of the specification). The deleted phrase is also superfluous as it simply describes a necessary property of practicing the process according to Claim 51 in the setting of Claim 55. Accordingly, the amendment adds no new matter.

Entry of the amendments is respectfully requested.

Drawings

Formal drawings are being prepared to comply with the Draftsperson's Review and will be submitted shortly.

Trademarks

The Examiner noted the use in Example 17 of the trademarks RNEASY and SARTOLON, which had not been previously described in the specification. Applicants have amended the paragraphs in Example 17 at p. 34, line 27-p. 35, line 30, to recite these trademarks in uppercase lettering with registration mark and to include an appropriate corresponding generic description of the materials covered by the particular marks. The amendments to the paragraphs in Example 17 of the specification provide a proper recitation of the trademarks according to MPEP § 608.01(v).

Formal Claim Objections Under 37 CFR § 1.75(c)

In the Office Action (Paper No. 9), the Examiner objected to Claims 5, 9-23, 31, and 50 as being in an improper form based on the prohibition against a multiple dependent claim serving

as the basis for another multiple dependent claim. As noted above, Applicants have amended Claims 3, 5, and 43 in a manner that eliminates such improper multiple dependencies.

The Examiner also objected to Claims 25 and 28, noting grammatical/typographical errors. Applicants have amended Claim 25 to recite the grammatically correct "released" instead of "release". Applicants have also amended Claim 28 to recite the grammatically correct "claim 26" instead of "claims 26". The amendments provide the formal corrections called for by the Examiner.

The amendments place the claims in proper form as required by the Examiner. Accordingly, the objections are rendered moot and the Examiner is requested to withdraw the objections.

Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 1-4, 24-30, and 32-50 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. Applicants traverse the rejections for the reasons provided below.

As noted above, Applicants have amended the claims to clearly cover a preferred process of the invention for isolating nucleic acids. The amendments also make the rejections moot.

The Examiner objected to recitation of the phrase "essentially in the same direction as the charging" in Claim 1 as a basis for rejecting Claims 1-4, 24-30, and 32-50. Applicants have amended Claim 1 (and thereby, claims depending therefrom) to remove the objected to phrase and to clearly recite essential steps of a process for isolating nucleic acids comprising charging a non-siliceous surface, which surface has two opposing sides, followed by immobilizing, releasing, and removing nucleic acids from the same side of the non-siliceous surface on which the nucleic acids were immobilized. Applicants submit that the amendment describes a preferred process of the invention in clear and definite terms to persons skilled in this art in accordance with 35 U.S.C. § 112, second paragraph. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejections.

The Examiner also rejected Claims 26 and 28-30 for lacking sufficient antecedent basis for recitation of "said immobilization buffer". As noted above, Applicants have amended Claim 26 to properly depend from Claim 5, which expressly provides the antecedent "an

immobilization buffer" for Claims 26 and 28-30. Accordingly, the Examiner is requested to reconsider and withdraw the rejections.

In the Office Action, Claim 27 was rejected as lacking sufficient antecedent basis for "the chaotropic agent". As amended, Claim 26 expressly recites a process according to Claim 5, wherein the immobilization buffer comprises "a" chaotropic agent, thereby provided the antecedent basis for subsequent recitation of the term in Claim 27. Accordingly, reconsideration and withdraw of the rejection is respectfully solicited.

The Examiner rejected Claims 27, 38, and 45 as being in improper form for Markush-style claiming. Applicants have amended Claims 27, 38, and 45 as indicated herein to place each of these claims in a standard Markush-style format. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejections.

The Examiner rejected Claims 28-30 and Claims 46-48 for recitation of the phrase "with other salts". In the course of amending the claims, Applicants have removed the phrase "alone or in combination with other salts" from Claims 28-30 and Claims 46-48 as superfluous to the preferred concentration ranges for an aqueous solution of a chaotropic agent that may be used for immobilizing nucleic acids in the claimed process of the invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejections.

The Examiner also rejected Claim 38 for reciting the phrase "characterized in that". In the process of amending Claim 38 to place the claim in a proper Markush-style format, Applicants removed the objected to phrase and inserted therefor the term "wherein". Accordingly, reconsider and withdrawal of the rejection is requested.

The Examiner rejected Claim 41 as lacking sufficient antecedent basis for recitation of the phrase "the pores". In the course of amending Claim 41 to place the claim in a proper Markush-style format, Applicants also amended the language to clearly indicate that the membrane used in the process according to any one of Claims 32 through 40 *has* pores, which have a range of diameters selected from a group of preferred diameter ranges. Applicants respectfully submit that persons skilled in this art would clearly understand the limitations of Claim 41 and therefore respectfully request that the Examiner reconsider and withdraw the rejections.

Claim 45 was rejected as lacking sufficient antecedent basis for recitation of "the chaotropic agent". Claim 45 depends from Claim 44. As mentioned above, Applicants amended

Claim 44 to depend directly from Claim 1, instead of canceled Claim 43, and to specifically cover the embodiment of Claim 1 wherein "a chaotropic agent is used for the immobilization of the nucleic acids". Accordingly, Claim 44 provides sufficient antecedent basis for "the" chaotropic agent recited in Claim 45, and the Examiner is respectfully requested to reconsider and withdraw the rejection.

Finally, the Examiner rejected Claim 55 as lacking sufficient antecedent basis for recitation of "said membranes". As noted above, Applicants have amended Claim 55 to clearly cover an embodiment of the process according to Claim 51, wherein "said process" (not "said membranes") is carried out in a particular format, i.e., in a plurality of isolation devices installed on a multi-well plate. The amendment provides a clear and logical syntax for claiming a particularly preferred embodiment of the process of Claim 51. Accordingly, Applicants submit that the rejection is now moot, and the Examiner is respectfully requested to withdraw the rejection.

Rejections Under 35 U.S.C. § 102

In the Office Action, the Examiner rejected Claims 1-3, 24, 26, 28-30, 32-34, and 36 under 35 U.S.C. § 102(b) as anticipated by Holmes et al. (*Mol. Gen. Genet., 204*: 108-114 (1986), hereinafter "Holmes"). Applicants respectfully traverse the rejection.

Holmes describes a method of isolating nucleic acids, which method is an alkaline elution assay for measuring single-stranded breaks in DNA from cells deposited and lysed on a stack of three polyvinyl chloride filters in a filter funnel equipped by a needle to peristalic pump (see, first column, p. 110 of Holmes). Detergent, salts, cell debris, and DNA binding proteins are washed through and collected in fractions from the bottom of the stack of filters in a step-wise procedure leaving a purified cellular DNA on the top of the stack of membranes. As noted by the Examiner, the DNA is subsequently released and collected in drop-wise manner in fractions from the bottom of the membranes. Holmes observed that by using the amounts and types of elution buffers and the drop-wise manner of collecting the DNA from the bottom of the filters, the DNA can be collected in various molecular weights and structures, i.e., with lower molecular weight single-stranded DNA eluting and collected first, followed by higher molecular weight single strands, then cross-linked DNA.

Although Applicants' review of the protocol in Holmes does not reveal a step involving use of a solution of a "3 M chaotropic agent" as mentioned in the Office Action, a clear and critical difference between Holmes' and Applicants' processes for isolating nucleic acids is that nucleic acids isolated according to Applicants' claimed process are immobilized on, released from, and removed from the *same* side of a non-siliceous surface (e.g., a membrane) and, thus, are not removed and then collected through or from the bottom of a surface or membrane as in Holmes. Thus, the method described by Holmes is clearly different from Applicants' claimed process. As Holmes clearly does not teach each and every element of Applicants' claimed process as required for anticipation (see, e.g., MPEP § 2131), Holmes does not anticipate the claims under 35 U.S.C. § 102(b).

In view of the above comments, Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

The Examiner also rejected Claims 1-3 and "2-30" [sic] under 35 U.S.C. § 102(b) as anticipated by Jakobi et al. (*Anal. Biochem., 175*: 196-201 (1988), hereinafter "Jakobi"). Applicants are not sure exactly which of the claims the Examiner rejected, however, Applicants respectfully traverse the rejection for the reasons provided below.

Jakobi describes a method of preparing lambda phage DNA released from phage particles deposited on GF/C glass fiber filters positioned in disposable syringes. The DNA of the phage particles is released by centrifuging a solution of 4 M sodium perchlorate/50% formamide through the filter. The DNA is then released by incubating the syringe with 0.1 X TE buffer, at 60-65°C for 15-30 minutes and then collected by, as noted by the Examiner, by centrifuging the DNA through the GF/C glass fiber filter and out of the syringe outlet (see, e.g., descriptions on pp. 197 and 199 of Jakobi). In contrast, nucleic acids isolated according to Applicants' claimed process are immobilized on, released from, and removed from the *same* side of a *non-siliceous* surface or membrane and, thus, are not removed and then collected through or from the bottom of a glass fiber filter as in Jakobi. Accordingly, the method described by Jakobi, which employs a siliceous filter and collects DNA passed through the siliceous filter, is clearly different from Applicants' claimed process. As Jakobi does not teach each and every element of Applicants' claimed process as required for anticipation (see, e.g., MPEP § 2131), Jakobi does not anticipate the claims under 35 U.S.C. § 102(b).

In view of the above comments, Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

Claims 1-4, 24-30, 32, 42, 51, 55, and 58 were rejected as anticipated under 35 U.S.C. § 102(b) by international publication No. WO 96/41810, published December 27, 1996 (hereinafter, "Progen"). For the reasons given below, Applicants respectfully traverse the rejection.

Progen describes a filter apparatus having a hollow membrane filter positioned above an ion exchange membrane and a method of using the filter apparatus for isolating DNA from a suspension cells. The method of Progen involves applying a suspension of cells to the filter apparatus having a hollow membrane filter, lysing the cells to release DNA, applying DNA released from the lysed cells to the ion exchange medium under the hollow membrane filter (see, e.g., p. 7, lines 16-30 and Figures 1 and 2 of Progen), releasing the DNA from the ion exchange medium, and collecting the released DNA through ion exchange medium from the bottom of the filter apparatus (see, e.g., p. 7, lines 31-32; p. 11, lines 1-6; p. 12, line 32-p. 13, line 4; in Example 1 at p. 13, line 29-p. 14, line 2; in Example 4 at p. 17, lines 1-2; in Example 5 at p. 18, lines 26-27; and in Example 6 at p. 19, lines 32-33 of Progen). Notably, Applicants' claimed process for isolating nucleic acids does not require or employ Progen's filter apparatus having a hollow membrane filter positioned above an ion exchange membrane. Neither does Applicants' claimed process involve collecting DNA through a membrane from the bottom of the filter apparatus described and demonstrated in Progen. As noted above, nucleic acids isolated according to Applicants' claimed are immobilized on, released from, and removed from one and the *same* side of a *non-siliceous* surface and, thus, are clearly not as described by Progen immobilized on one side of a filter and then collected through and from the bottom of the other side of the filter. Accordingly, the method described by Progen is clearly different from Applicants' claimed process. As Progen clearly does not teach each and every element of Applicants' claimed process as required for anticipation (see, e.g., MPEP § 2131), Progen does not anticipate the claims under 35 U.S.C. § 102(b).

For the above reasons, Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

Claims 1-4, 24-30, 32-42, 52-55, and 58 were rejected as anticipated by U.S. Patent No. 6,258,531 (hereinafter the "Bienhaus") under 35 U.S.C. § 102(e). Applicants traverse the rejection for the reasons explained below.

Bienhaus describes an intricate apparatus and method of using the apparatus for isolating a biological material. The apparatus comprises several components, including a hollow structural form having a bottom (or first) opening and a top (or second) opening, which is filled with a "compressible porous matrix" to which is bound a biological material of interest. When the biological material is a nucleic acid, the nucleic acid is bound to a compressible glass fleece matrix. The nucleic acid may be added to the glass fleece matrix through one of the openings of the hollow structural form. The hollow structural form containing nucleic acid bound to the glass fleece matrix can then be inserted into an "elution vessel" containing an elution buffer, which then enters the hollow structure through the bottom opening to submerge the glass fleece matrix and release the nucleic acid from the glass fleece matrix. A piston is then inserted into the top (or second) opening of the hollow structure and forced downward, compressing the glass fleece and permitting the eluted DNA to be squeezed out of the matrix and into an interior cylindrical bore of the piston (see, e.g., Example 2 at col. 9, line 25-col. 10, line 28 for demonstration of isolating nucleic acid).

In contrast to Bienhaus, Applicants' claimed process does not employ the hollow structural form, elution vessel, and hollow piston described by Bienhaus. Furthermore, Applicants' process for isolating nucleic acids employs a non-siliceous surface that has two opposing sides, not a compressible porous matrix, such as a glass fleece matrix that must be compressed to squeeze out and collect nucleic acid released from the matrix. Clearly, Bienhaus does not teach each and every element of Applicants' claimed process as required for anticipation (see, e.g., MPEP § 2131). Accordingly, Bienhaus does not anticipate the claims under 35 U.S.C. § 102(e), and the Examiner is respectfully requested to reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. § 103

In the Office Action, the Examiner rejected Claims 1-4, 24-30, 32-42, 52-55, and 58 under 35 U.S.C. § 103(a) as obvious over each of Holmes, Jakobi, Progen, and Bienhaus in combination with U.S. Patent No. 5,004,543 (hereinafter, "Pluskal"). Claims1-4, 24-30, 32-49, 52-55, and 58 were rejected as obvious over the previous combination of documents in further

combination with U.S. Patent No. 5,658,548 (hereinafter, "Padhye"). For the reasons provided below, Applicants respectfully traverse the rejections.

At the outset, Applicants note that none of the documents relied on by the Examiner provide any teaching or motivation to be combined to make Applicants' claimed process. In reviewing the rejections and cited documents, Applicants respectfully submit that at no place in these rejections has the Examiner provided a proper basis for concluding that a person of ordinary skill in the art would combine the teachings of the cited documents as the Examiner has done to arrive at Applicants' claimed process.

The legal standard for rejecting claims as obvious over a combination of references was reviewed by the Court of Appeals for the Federal Circuit in *In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). As the court in *Kotzab* noted:

> "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, **guided only by the prior art references and the then-accepted wisdom in the field**. See *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one 'to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.' *Id.* (quoting *W.L. Gore & Assocs. Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed.Cir.1983)).
>
> "Most if not all inventions arise from a combination of old elements. *See In re Rouffett*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed.Cir.1998). Thus, every element of a claimed invention may often be found in the prior art. See *Id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. See *Id.* Rather, **to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant**. *See In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed.Cir.1998): *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed.Cir.1984). . . .
>
> "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved.

> *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. In addition, the teaching, motivation or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. *See WMS Gaming, Inc. v. International Game Tech.*, 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). . . . Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617." (*In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000) (emphasis added)).

As noted above, the motivation to combine documents to make a *prima facie* case of obviousness may derive from many sources, however, the range of possible sources that may serve as evidence for a motivation to combine references "does not diminish the requirement for **actual evidence**. That is, the showing [of a motivation to combine] must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617, 1999 WL 246572 (Fed. Cir. 1999) (emphasis added). Furthermore, "[b]road conclusory statements standing alone are not 'evidence'."

Notwithstanding a lack of such required evidence of a motivation to combine the cited documents, Applicants submit that even if combined as set forth in the Office Action, the combined documents still fail to provide a person of ordinary skill in this art with Applicants' claimed process for isolating nucleic acids for reasons given below.

Holmes, Jakobi, Progen, and Bienhaus were considered and distinguished from Applicants' invention as described above. Briefly: Holmes describes a method of measuring breaks in DNA released from cells in which the DNA is eluted from and collected in a drop-wise from the bottom of a stack of polyvinyl chloride filters. Jakobi describes depositing phage DNA on a GF/C glass fiber filter and subsequently centrifuging the DNA through the glass filter for collection. Progen describes an apparatus and method of use thereof having a hollow membrane filter positioned above an ion exchange medium such that DNA is released from cells and is eventually collected through the bottom of the ion exchange medium. Bienhaus describes an intricate, multi-component apparatus and method of use thereof that may be used to isolate DNA in which DNA is bound to the strands of a compressible glass fiber matrix, which is then submerged in an elution buffer and compressed to squeeze the released DNA out of the matrix. Nowhere do these documents alone or in combination teach or suggest Applicants' process for isolating nucleic acids wherein a non-siliceous surface having two opposing sides is charged on

one side of the non-siliceous suface with the nucleic acids, which are then immobilized on, released from, and removed from the *same* side of the non-siliceous surface. Considered together, Holmes, Jakobi, Progen, and Bienhaus describe collecting DNA by employing siliceous membranes (Jakobi, Bienhaus, and preferred in Progen), or a specific multi-component apparatus (Progen, Bienhaus), or passage of DNA through a membrane and collection from the bottom of the membrane or apparatus (Holmes, Jakobi, Progen); *all of which are clearly outside of Applicants' claimed process*.

Pluskal describes a hydrophobic membrane having a cross-linked, cationic charge-modifying coating to provide improved DNA binding for use in various blotting protocols. Pluskal describes the superior ability over prior art membranes to *retain* DNA blotted on the membrane. The superior retention of DNA on a membrane of Pluskal over prior art membranes is demonstrated under standard conditions employed to detect DNA blotted on a membrane with a radiolabeled nucleic acid probe as well as under the drastic conditions typically employed to subsequently strip the labeled nucleotide probe hybridized to DNA blotted and retained on the membrane (see, e.g., Examples 2-5 of Pluskal). Thus, Pluskal directs persons of ordinary skill in this art to a method of *increased retention* of DNA on a membrane for blotting protocols, not to the use of a membrane to collection and isolation of DNA according to Applicants' invention. Accordingly, Pluskal does not cure the deficiencies in any of the combinations of documents in the Office Action to provide Applicants' process of isolating nucleic acids. Only Applicants' disclosure provides persons of ordinary skill in this art with the necessary teaching and guidance for practicing the claimed process in which nucleic acids are isolated by immobilization on and subsequent removable from the same side of a non-siliceous surface.

Padhye clearly fails to advance any of the combinations set forth in the Office Action because Padhye expressly describes purification of nucleic acids that are greater than about 50 bases in length using certain mixtures of silica gel and glass particles. Nowhere does Padhye provide a teaching or suggestion of Applicants' process or advance the combination of documents set forth in the Office Action to arrive at Applicants' process, which expressly employs a non-siliceous surface.

Applicants respectfully submit that the above comments make clear that even if the documents are combined as set forth in the Office Action, there is no teaching or suggestion of

Applicants' claimed process for isolating nucleic acids. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejections.

In view of all of the above comments, Applicants respectfully submit that the claims as amended herein are in proper form for allowance. Accordingly, Applicants respectfully request that the Examiner enter the amendments to the specification and claims, reconsider and withdraw the rejections, and pass Claims 1-5, 9-41, 44-49, 51-55, and 58-64 to allowance.

Respectfully submitted,

Thomas R. Berka

Thomas R. Berka, Ph.D. (Reg. No. 39,606)
Leon R. Yankwich (Reg. No. 30,237)
Attorneys for Applicants
YANKWICH & ASSOCIATES
201 Broadway
Cambridge, Massachusetts 02139
telephone: (617) 374-3700
telecopier: (617) 374-0055

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September 16, 2002
date

Stephanie L. Leicht
Stephanie L. Leicht

AMENDED PARAGRAPHS IN U.S. SERIAL NO. 09/536,736

(marked up paragraphs showing deletion of terms by ~~strikethrough~~ and added terms by underling)

According to Example 3, plastic columns were assembled with commercially available membranes (Pall Gelman Sciences, Hydrolon with a pore size of 1.2 or 3 µm; Sartorius, ~~Sartolon~~ SARTOLON® polyamide filter membrane with a pore size of 0.45 µm).

For isolation of RNA, two different starting materials were used:

1) total RNA from liver (mouse) in an aqueous solution; the purification of total RNA and the elution were carried out as described in Example 4; and
2) 5×10^5 HeLa cells, the purification of total RNA and the elution were carried out as described in Example 3.

For each test, 20 ng of isolated total RNA were used. As a control, RNA purified using ~~RNeasy~~ RNEASY® RNA isolation-Kits (Qiagen GmbH) and a sample without RNA were used.

A RT-PCR was performed with these samples under standard conditions. For amplification two different primer pairs were used for the ß-Actin. A 150 Bp-sized fragment served as proof of sensitivity, a 1.7 kBp-sized fragment assessed the integrity of the RNA. From the RT-reaction, 1 µl was removed and transferred to the subsequent PCR. 25 cycles were performed for the small fragment and 27 cycles for the large fragment. The annealing temperature was 55°C. The amplified samples were subsequently placed on a non-denaturing gel and analyzed.

For the 20 ng volume used of total RNA isolated in the process described above, the corresponding DNA-fragments can be demonstrated in the RT-PCR. When using total RNA from mouse liver, no transcript can be demonstrated, as the conditions used here were adjusted to human ß-Actin. The control specimens which contain no RNA did not produce any signals. Figure 7 shows ethidium bromide stained gels of an electrophoretic separation of RT-reactions.

Figure 7A: Lane 1 to 8: RT-PCR of a 150 Bp-fragment;

Lane 1, 2: RNA from an aqueous solution purified with the Hydrolon 1.2 µm membrane;

Lane 3, 4: RNA from HeLa cells purified with the ~~Sartolon~~ SARTOLON® polyamide filter membrane;

Lane 5, 6: RNA from HeLa cells purified with the Hydrolon 3 µm membrane;

Lane 7: RNA purified by way of ~~RNeasy~~ RNEASY® RNA isolation-Mini-Kit;

Lane 8: Control without RNA.

Figure 7B: Lane 1 to 8: RT-PCR of a 1.7 kBp-fragment;

Lane 1, 2: RNA from an aqueous solution purified with the Hydrolon 1.2 µm membrane;

Lane 3, 4: RNA from HeLa cells purified with the ~~Sartolon~~ SARTOLON® polyamide filter membrane;

Lane 5, 6: RNA from HeLa cells purified with the Hydrolon 3 µm membrane;

Lane 7: RNA purified by way of ~~RNeasy~~ RNEASY® RNA isolation-Mini-Kit;

Lane 8: Control without RNA.

AMENDED CLAIMS IN U.S. SERIAL NO. 09/536,736

(marked up claims showing deletions by ~~strikethrough~~, additions by underlining, and new claims as indicated)

1. (amended) A process for isolating nucleic acids comprising the following steps:
   - charging a non-siliceous surface from a given direction with nucleic acids, wherein said non-siliceous surface has two opposing sides;
   - immobilizing the nucleic acids on one side of the non-siliceous surface;
   - releasing the immobilized nucleic acids from the non-siliceous surface; and
   - removing the released nucleic acids from the same side of the non-siliceous surface ~~, essentially in the same direction of the charging~~ on which the nucleic acids were immobilized.

2. (amended) The process according to claim 1, wherein the non-siliceous surface is oriented so that one of the two opposing sides of the non-siliceous surface is on top of the other side and so that the charging and removal of the nucleic acids takes place from the top opposing side of the non-siliceous surface.

3. (amended) The process according to claim 1 ~~or 2~~, wherein, between the immobilization and release steps, a washing of the immobilized nucleic acids with at least one washing buffer takes place.

4. (amended) The process according to claim 3, wherein the washing includes the following steps for each washing buffer:
   - transferring a predetermined amount of washing buffer to the non-siliceous surface, and -
   - drawing the washing buffer through the non-siliceous surface by suction.

5. (amended) The process according to claim 1 further comprising ~~any of claims 1, 2 or 4, wherein the charging and immobilization of the nucleic acids includes~~ the following steps:
   - mixing of the nucleic acids with an immobilization buffer;
   - charging of the nucleic acids with the immobilization buffer on to the non-siliceous

surface;

- drawing the fluid components through the surface ~~essentially in the direction of the charging~~.

9. (amended) The process according to claim 1 ~~any of claims 1, 2 or 4~~, characterized by the fact that between the release and the removal steps ~~at least one of the following steps is also carried out:~~

~~—carrying out of~~ at least one chemical reaction is carried out on the nucleic acids ~~;~~

~~immobilization of the nucleic acids on the surface; and~~

~~release of the immobilized nucleic acids from the surface~~.

13. (amended) The process according to claim 5, wherein said immobilization buffer includes aqueous solutions of salts of ~~from~~ monobasic or polybasic or polyfunctional organic acids with alkaline or alkaline earth metals.

14. (amended) The process according to claim 13, wherein said aqueous solutions of salts of polyfunctional organic acids with alkaline or alkaline earth metals ~~immobilization buffer~~ includes aqueous solutions of salts of sodium, potassium, or magnesium with organic dicarboxylic acids.

16. (amended) The process according to claim 13, wherein said aqueous solutions of salts of polyfunctional organic acids with alkaline or alkaline earth metals ~~immobilization buffer~~ includes aqueous solutions of salts of sodium or potassium in combination with hydroxycarboxylic or polyhydroxycarboxylic acid.

Cancel ~~23. The process according to claim 3, wherein the washing step is carried out using a salt solution or a buffer solution pursuant to any one of claims 4 through 22~~.

25. (amended) The process according to claim 1, wherein the nucleic acids immobilized on the surface are released using water.

26. (amended) The process according to claim 5 ~~3~~, wherein said immobilization buffer comprises an aqueous solution of a ~~includes~~ chaotropic agent~~s~~.

27. (amended) The process according to claim 26, wherein the chaotropic agent is selected from the group consisting of trichloro-acetates, thiocyanates, perchlorates, iodides, guanidinium hydrochloride, guanidinium isothiocyanate, and urea.

28. (amended) The process according to claim~~s~~ 26, wherein said immobilization buffer comprises a 0.01-molar to 10-molar aqueous solution~~s~~ of the chaotropic agent~~s, alone or in combination with other salts~~.

29. (amended) The process according to claim 28, wherein said immobilization buffer comprises a 0.1-molar to 7-molar aqueous solution~~s~~ of the chaotropic agent~~s, alone or in combination with other salts~~.

30. (amended) The process according to claim 29, wherein said immobilization buffer comprises a 0.2- molar to 5-molar aqueous solution~~s~~ of the chaotropic agent~~s, alone or in combination with other salts~~.

31. (amended) The process according to any one of claims 26 through 30, wherein said immobilization buffer comprises an aqueous solution of sodium perchlorate, guanidinium hydrochloride, guanidinium isothiocyanate, sodium iodide, or potassium iodide ~~are used for the immobilization of nucleic acids~~.

38. (amended) The process according to claim 36, wherein ~~characterized by the fact that~~ the membrane is coated with a hydrophobic coating agent selected from the group consisting of paraffins, waxes, metallic soaps, ~~optionally in admixture with aluminum or zirconium salts,~~ quaternary organic compounds, urea derivates, lipid-modified melamine resins, ~~silicones,~~ organic zinc compounds, and glutaric dialdehyde.

41. (amended) The process according to any one ~~on~~ of claims 32 through 40, wherein ~~the pores in~~ the membrane has pores which have a range of diameters selected from the group consisting of 0.001 to 50 micrometers, ~~preferably from~~ 0.01 to 20 micrometers, and ~~most preferably~~ from 0.05 to 10 micrometers.

Cancel ~~42. The process according to claim 1, wherein the surface is a hydrophobic fleece.~~

Cancel ~~43. The process according to claim 42, wherein the fleece is a silica gel fleece.~~

44. (amended) The process according to claim 1 ~~43~~, wherein a chaotropic agent~~s~~ is ~~are~~ used for the immobilization of the nucleic acids.

45. (amended) The process according to claim 44, wherein the chaotropic agent is selected from the group consisting of trichloro-acetates, thiocyanates, perchlorates, iodides, guanidinium hydrochloride, guanidinium isothiocyanate, and urea.

46. (amended) The process according to claim 44, wherein a 0.01-molar to 10-molar aqueous solution~~s~~ of the chaotropic agent~~s, alone or in combination with other salts, are~~ is used for the immobilization of nucleic acids.

47. (amended) The process according to claim 46, wherein a 0.1-molar to 7-molar aqueous solution~~s~~ of the chaotropic agent~~s, alone or in combination with other salts, are~~ is used for the immobilization of nucleic acids.

48. (amended) The process according to claim 47, wherein a 0.2-molar to 5-molar aqueous solution~~s~~ of the chaotropic agent~~s, alone or in combination with other salts, are~~ is used for the immobilization of nucleic acids.

49. (amended) The process according to any one of claims 44 through 48, wherein ~~an aqueous solution~~ the chaotropic agent is selected from the group consisting of sodium perchlorate,

guanidinium hydrochloride, guanidinium isothiocyanate, sodium iodide, and ~~or~~ potassium iodide ~~are used for the immobilization of nucleic acids~~.

51. (amended) A process for isolating nucleic acids comprising immobilization of nucleic acids on one side of a membrane, followed by release of the nucleic acids and collection of the nucleic acids from the same side of the membrane on which the nucleic acids ~~they~~ were immobilized.

54. (amended) The process according to claim 51, wherein the membrane is a hydrophilic membrane, which is coated with a hydrophobic coating agent selected from the group consisting of paraffins, waxes, metallic soaps, ~~optionally in admixture with aluminum or zirconium salts,~~ quaternary organic compounds, urea derivates, lipid-modified melamine resins, ~~silicones,~~ organic zinc compounds, and glutaric dialdehyde.

55. (amended) The process according to claim 51, wherein said process for isolating nucleic acids is carried out in a plurality of ~~said membranes are incorporated in~~ isolation devices installed on a multi-well plate.

59. (new) The process according to claim 3, wherein the washing step is carried out using a an aqueous solution of a salt of an alkaline or alkaline earth metal with a mineral acid.

60. (new) The process according to claim 3, wherein the washing step is carried out using a an aqueous solution of a salt from a monobasic, polybasic, or polyfunctional organic acid with an alkaline or alkaline earth metal.

61. (new) The process according to claim 3, wherein the washing step is carried out using an aqueous solution of a chaotropic agent.

62. (new) The process according to claim 3, wherein the washing step is carried out using a hydroxyl derivative of an aliphatic or acyclic saturated or unsaturated hydrocarbon.

63. (new) The process according to claim 3, wherein the washing step is carried out using a phenol or a polyphenol.

64. (new) The process according to claim 38 or claim 54, wherein said metallic soaps are in admixture with aluminum or zirconium salts.

Complete Set of Amended Claims

1. (amended) A process for isolating nucleic acids comprising the following steps:
   - charging a non-siliceous surface from a given direction with nucleic acids, wherein said non-siliceous surface has two opposing sides;
   - immobilizing the nucleic acids on one side of the non-siliceous surface;
   - releasing the immobilized nucleic acids from the non-siliceous surface; and
   - removing the released nucleic acids from the same side of the non-siliceous surface on which the nucleic acids were immobilized.

2. (amended) The process according to claim 1, wherein the non-siliceous surface is oriented so that one of the two opposing sides of the non-siliceous surface is on top of the other side and so that the charging and removal of the nucleic acids takes place from the top opposing side of the non-siliceous surface.

3. (amended) The process according to claim 1, wherein, between the immobilization and release steps, a washing of the immobilized nucleic acids with at least one washing buffer takes place.

4. (amended) The process according to claim 3, wherein the washing includes the following steps for each washing buffer:
   - transferring a predetermined amount of washing buffer to the non-siliceous surface, and
   - drawing the washing buffer through the non-siliceous surface by suction.

5. (amended) The process according to claim 1 further comprising the following steps:
   - mixing of the nucleic acids with an immobilization buffer;
   - charging of the nucleic acids with the immobilization buffer on to the non-siliceous surface;
   - drawing the fluid components through the surface.

9. (amended) The process according to claim 1, characterized by the fact that between the release and the removal steps at least one chemical reaction is carried out on the nucleic acids.

10. The process according to claim 5, wherein said immobilization buffer includes aqueous solutions of salts of alkaline and alkaline earth metals with mineral acids.

11. The process according to claim 10, wherein said immobilization buffer includes alkaline or alkaline earth halogenides or sulfates.

12. The process according to claim 11, wherein said immobilization buffer includes halogenides of sodium or potassium or magnesium sulfate.

13. (amended) The process according to claim 5, wherein said immobilization buffer includes aqueous solutions of salts of monobasic or polybasic or polyfunctional organic acids with alkaline or alkaline earth metals.

14. (amended) The process according to claim 13, wherein said aqueous solutions of salts of polyfunctional organic acids with alkaline or alkaline earth metals includes aqueous solutions of salts of sodium, potassium, or magnesium with organic dicarboxylic acids.

15. The process according to claim 14, wherein said organic dicarboxylic acid is oxalic acid, malonic acid, or succinic acid.

16. (amended) The process according to claim 13, wherein said aqueous solutions of salts of polyfunctional organic acids with alkaline or alkaline earth metals includes aqueous solutions of salts of sodium or potassium in combination with hydroxycarboxylic or polyhydroxycarboxylic acid.

17. The process according to claim 16, wherein said polyhydroxycarboxylic acid is citric acid.

18. The process according to claim 5, wherein said immobilization buffer includes hydroxyl derivates of aliphatic or acyclic saturated or unsaturated hydrocarbons.

19. The process according to claim 18, wherein said hydroxyl derivatives are C1-C5 alkanols.

20. The process according to claim 19, wherein said alkanols are selected from methanol, ethanol, n-propanol, tert.-butanol and pentanols.

21. The process according to claim 18, wherein said hydroxyl derivative is an aldite.

22. The process according to claim 5, wherein said immobilization buffer includes a phenol or polyphenol.

23. (amended) The process according to claim 3, wherein the washing step is carried out using an aqueous solution of a salt from a monobasic or polybasic or polyfunctional organic acid with an alkaline or alkaline earth metal.

24. The process according to claim 1, wherein the releasing step is carried out using an aqueous salt or buffer solution.

25. (amended) The process according to claim 1, wherein the nucleic acids immobilized on the surface are released using water.

26. (amended) The process according to claim 5, wherein said immobilization buffer comprises an aqueous solution of a chaotropic agent.

27. (amended) The process according to claim 26, wherein the chaotropic agent is selected from the group consisting of trichloro-acetates, thiocyanates, perchlorates, iodides, guanidinium hydrochloride, guanidinium isothiocyanate, and urea.

28. (amended) The process according to claim 26, wherein said immobilization buffer comprises a 0.01-molar to 10-molar aqueous solution of the chaotropic agent.

29. (amended) The process according to claim 28, wherein said immobilization buffer comprises a 0.1-molar to 7-molar aqueous solution of the chaotropic agent.

30. (amended) The process according to claim 29, wherein said immobilization buffer comprises a 0.2- molar to 5-molar aqueous solution of the chaotropic agent.

31. (amended) The process according to any one of claims 26 through 30, wherein said immobilization buffer comprises an aqueous solution of sodium perchlorate, guanidinium hydrochloride, guanidinium isothiocyanate, sodium iodide, or potassium iodide.

32. The process according to claim 1, wherein the surface is a membrane.

33. The process according to claim 32, wherein the membrane is a hydrophobic membrane.

34. The process according to claim 33, wherein the hydrophobic membrane is made of a polymer with polar groups.

35. The process according to claim 32, wherein the membrane is a hydrophilic membrane with a hydrophobisized surface.

36. The process according to claim 32, wherein the membrane is composed of a polymeric material selected from the group consisting of nylon, a polysulfone, polyether sulfone, polycarbonate, polyacrylate, acrylic acid copolymer, polyurethane, polyamide, polyvinyl chloride, polyfluorocarbonate, polytetrafluoroethylene, polyvinylidene fluoride, polyvinylidene difluoride, polyethylene tetrafluoroethylene copolymerisate, polyethylene chlorotrifluoroethylene copolymerisate, and polyphenylene sulfide.

37. The process according to claim 36, wherein the membrane consists of hydrophobisized nylon.

38. (amended) The process according to claim 36, wherein the membrane is coated with a hydrophobic coating agent selected from the group consisting of paraffins, waxes, metallic soaps, quaternary organic compounds, urea derivates, lipid-modified melamine resins, organic zinc compounds, and glutaric dialdehyde.

39. The process according to claim 32, wherein the membrane is a hydrophilic or hydrophilized membrane.

40. The process according to claim 39, wherein the membrane is composed of hydrophilized nylon, polyether sulfone, polycarbonate, polyacrylate, acrylic acid copolymer, polyurethane, polyamide, polyvinyl chloride, polyfluorocarbonate, polytetrafluoroethylene, polyvinylidene fluoride, polyvinylidene difluoride, polyethylene tetrafluoroethylene copolymerisate, polyethylene chlorotrifluoroethylene copolymerisate, or polyphenylene sulfide.

41. (amended) The process according to any one of claims 32 through 40, wherein the membrane has pores which have a range of diameters selected from the group consisting of 0.001 to 50 micrometers, 0.01 to 20 micrometers, and from 0.05 to 10 micrometers.
have a diameter range selected from the group consisting of 0.001 to 50 micrometers, 0.01 to 20 micrometers, and from 0.05 to 10 micrometers.

44. (amended) The process according to claim 1, wherein a chaotropic agent is used for the immobilization of the nucleic acids.

45. (amended) The process according to claim 44, wherein the chaotropic agent is selected from the group consisting of trichloro-acetates, thiocyanates, perchlorates, iodides, guanidinium hydrochloride, guanidinium isothiocyanate, and urea.

46. (amended) The process according to claim 44, wherein a 0.01-molar to 10-molar aqueous solution of the chaotropic agent is used for the immobilization of nucleic acids.

47. (amended) The process according to claim 46, wherein a 0.1-molar to 7-molar aqueous solution of the chaotropic agent is used for the immobilization of nucleic acids.

48. (amended) The process according to claim 47, wherein a 0.2-molar to 5-molar aqueous solution of the chaotropic agent is used for the immobilization of nucleic acids.

49. (amended) The process according to any one of claims 44 through 48, wherein the chaotropic agent is selected from the group consisting of sodium perchlorate, guanidinium hydrochloride, guanidinium isothiocyanate, sodium iodide, and potassium iodide.

51. (amended) A process for isolating nucleic acids comprising immobilization of nucleic acids on one side of a membrane, followed by release of the nucleic acids and collection of the nucleic acids from the same side of the membrane on which the nucleic acids were immobilized.

52. The process according to claim 51, wherein the membrane is composed of a material selected from the group consisting of nylon, polysulfone, polyether sulfone, polycarbonate, polyacrylate, acrylic acid copolymer, polyurethane, polyamide, polyvinyl chloride, polyfluorocarbonate, polytetrafluoroethylene, polyvinylidene fluoride, polyvinylidene difluoride, polyethylene tetrafluoroethylene copolymerisate, polyethylene chlorodifluoroethylene copolymerisate, and polyphenylene sulfide.

53. The process according to claim 52, wherein the membrane is a hydrophobisized nylon membrane.

54. (amended) The process according to claim 51, wherein the membrane is a hydrophilic membrane, which is coated with a hydrophobic coating agent selected from the group consisting of paraffins, waxes, metallic soaps, quaternary organic compounds, urea derivates, lipid-modified melamine resins, organic zinc compounds, and glutaric dialdehyde.

55. (amended) The process according to claim 51, wherein said process for isolating nucleic acids is carried out in a plurality of isolation devices installed on a multi-well plate.

58. The process according to one of claims 51 through 55, wherein the immobilization of nucleic acids takes place at a pH of from 3 to 11.

59. (new) The process according to claim 3, wherein the washing step is carried out using a an aqueous solution of a salt of an alkaline or alkaline earth metal with a mineral acid.

60. (new) The process according to claim 3, wherein the washing step is carried out using a an aqueous solution of a salt from a monobasic, polybasic, or polyfunctional organic acid with an alkaline or alkaline earth metal.

61. (new) The process according to claim 3, wherein the washing step is carried out using an aqueous solution of a chaotropic agent.

62. (new) The process according to claim 3, wherein the washing step is carried out using a hydroxyl derivative of an aliphatic or acyclic saturated or unsaturated hydrocarbon.

63. (new) The process according to claim 3, wherein the washing step is carried out using a phenol or a polyphenol.

64. (new) The process according to claim 38 or claim 54, wherein said metallic soaps are in admixture with aluminum or zirconium salts.